



PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

(Chapter II of the Patent Cooperation Treaty)

(PCT Article 36 and Rule 70)

| Applicant's or agent's file reference<br>101009-1 WO   |             | <b>FOR FURTHER ACTION</b>  |  | See Form PCT/PEAA416   |                 |                |     |       |             |      |
|--|-------------|--|--|--|-----------------|----------------|-----|-------|-------------|------|
| International application No.<br>PCT/GB2004/001272   |             | International filing date (day/month/year)<br>23.03.2004                   |  | Priority date (day/month/year)<br>29.03.2003   |                 |                |     |       |             |      |
| International Patent Classification (IPC) or national classification and IPC<br>C12Q1/18   |             |  |  |  |                 |                |     |       |             |      |
| Applicant<br>ASTRAZENECA AB et al.   |             |  |  |  |                 |                |     |       |             |      |
| <p>1. This report is the international preliminary examination report, established by this International Preliminary Examining Authority under Article 35 and transmitted to the applicant according to Article 36.</p> <p>2. This REPORT consists of a total of 7 sheets, including this cover sheet.</p> <p>3. This report is also accompanied by ANNEXES, comprising:</p> <p>a. <input type="checkbox"/> sent to the applicant and to the International Bureau a total of sheets, as follows:</p> <p><input type="checkbox"/> sheets of the description, claims and/or drawings which have been amended and are the basis of this report and/or sheets containing rectifications authorized by this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions).</p> <p><input type="checkbox"/> sheets which supersede earlier sheets, but which this Authority considers contain an amendment that goes beyond the disclosure in the international application as filed, as indicated in item 4 of Box No. I and the Supplemental Box.</p> <p>b. <input type="checkbox"/> (sent to the International Bureau only) a total of (indicate type and number of electronic carrier(s)) , containing a sequence listing and/or tables related thereto, in computer readable form only, as indicated in the Supplemental Box Relating to Sequence Listing (see Section 802 of the Administrative Instructions).</p> |             |  |  |  |                 |                |     |       |             |      |
| <p>4. This report contains indications relating to the following items:</p> <p><input checked="" type="checkbox"/> Box No. I Basis of the opinion</p> <p><input type="checkbox"/> Box No. II Priority</p> <p><input checked="" type="checkbox"/> Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability</p> <p><input type="checkbox"/> Box No. IV Lack of unity of invention</p> <p><input checked="" type="checkbox"/> Box No. V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement</p> <p><input checked="" type="checkbox"/> Box No. VI Certain documents cited</p> <p><input type="checkbox"/> Box No. VII Certain defects in the international application</p> <p><input type="checkbox"/> Box No. VIII Certain observations on the international application</p>   |             |  |  |  |                 |                |     |       |             |      |
| Date of submission of the demand<br><br>22.09.2004   |             | Date of completion of this report<br><br>18.02.2005                        |  | <table border="1"><thead><tr><th>CODE</th><th>DATE</th><th>NTD</th></tr></thead><tbody><tr><td>ANKOM</td><td>22 FEB 2005</td><td>GIPS</td></tr></tbody></table>                                    | CODE            | DATE           | NTD | ANKOM | 22 FEB 2005 | GIPS |
| CODE   | DATE        | NTD  |  |  |                 |                |     |       |             |      |
| ANKOM  | 22 FEB 2005 | GIPS   |  |  |                 |                |     |       |             |      |
| Name and mailing address of the international preliminary examining authority:<br><br> European Patent Office<br>D-80298 Munich<br>Tel. +49 89 2399 - 0 Tx: 523656 epmu d<br>Fax: +49 89 2399 - 4465  |             | Authorized Officer<br><br>Bassias, I<br><br>Telephone No. +49 89 2399-8106 |  | <table border="1"><tbody><tr><td>DATA<br/>ENTERED</td></tr><tr><td>FINAL<br/>CHECK</td></tr></tbody></table>  | DATA<br>ENTERED | FINAL<br>CHECK |     |       |             |      |
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| FINAL<br>CHECK   |             |  |  |  |                 |                |     |       |             |      |

# INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

International application No.  
PCT/GB2004/001272

## Box No. I Basis of the report

1. With regard to the **language**, this report is based on the international application in the language in which it was filed, unless otherwise indicated under this item.
  - ☐ This report is based on translations from the original language into the following language, which is the language of a translation furnished for the purposes of:
    - ☐ international search (under Rules 12.3 and 23.1(b))
    - ☐ publication of the international application (under Rule 12.4)
    - ☐ international preliminary examination (under Rules 55.2 and/or 55.3)
2. With regard to the **elements\*** of the international application, this report is based on *(replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report)*:

### Description, Pages

1-14 as originally filed

### Claims, Numbers

1-12 as originally filed

### Drawings, Sheets

1/7-7/7 as originally filed

- ☐ a sequence listing and/or any related table(s) - see Supplemental Box Relating to Sequence Listing
3. ☐ The amendments have resulted in the cancellation of:
    - ☐ the description, pages
    - ☐ the claims, Nos.
    - ☐ the drawings, sheets/figs
    - ☐ the sequence listing (*specify*):
    - ☐ any table(s) related to sequence listing (*specify*):
  4. ☐ This report has been established as if (some of) the amendments annexed to this report and listed below had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).
    - ☐ the description, pages
    - ☐ the claims, Nos.
    - ☐ the drawings, sheets/figs
    - ☐ the sequence listing (*specify*):
    - ☐ any table(s) related to sequence listing (*specify*):

\* If item 4 applies, some or all of these sheets may be marked "superseded."

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**Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability**

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1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application,

☒ claims Nos. 1-3

because:

☐ the said international application, or the said claims Nos. relate to the following subject matter which does not require an international preliminary examination (specify):

☐ the description, claims or drawings (*indicate particular elements below*) or said claims Nos. are so unclear that no meaningful opinion could be formed (*specify*):

☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

☒ no international search report has been established for the said claims Nos. 1-3

☐ the nucleotide and/or amino acid sequence listing does not comply with the standard provided for in Annex C of the Administrative Instructions in that:

the written form

☐ has not been furnished

☐ does not comply with the standard

the computer readable form

☐ has not been furnished

☐ does not comply with the standard

☐ the tables related to the nucleotide and/or amino acid sequence listing, if in computer readable form only, do not comply with the technical requirements provided for in Annex C-*bis* of the Administrative Instructions.

☒ See separate sheet for further details

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**Box No. V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement**

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1. Statement

|                               |             |      |
|-------------------------------|-------------|------|
| Novelty (N)                   | Yes: Claims | 4-12 |
|                               | No: Claims  | -    |
| Inventive step (IS)           | Yes: Claims | -    |
|                               | No: Claims  | 4-12 |
| Industrial applicability (IA) | Yes: Claims | 4-12 |
|                               | No: Claims  | -    |

2. Citations and explanations (Rule 70.7):

**see separate sheet**

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**Box No. VI Certain documents cited**

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1. Certain published documents (Rule 70.10)

and / or

2. Non-written disclosures (Rule 70.9)

**see separate sheet**

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(SEPARATE SHEET)**

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**Re Item III**

1. No international search report has been established for claims 1-3 and consequently said claims are not subject of the present international preliminary examination (Rule 66.1(e) PCT).

The reasons why claims 1-3 could not be searched are given below:  
Present claims 1-3 are so broad and unclear that a meaningful search over the whole scope of the claims is not possible. The method of claim 1 is not limited to a specific microorganism but refers to ANY microorganism. Furthermore, not a specific metabolic pathway has to be inhibited but ANY kind of metabolic pathway essential for viability. The expression "metabolic pathway ESSENTIAL FOR VIABILITY" is per se not clear in the sense of Article 6 PCT. When a pathway is essential depends very much on the growing conditions of the microorganism. Is an essential "product" missing in the growing medium and the microorganism is able to synthesize said "product" then the biosynthesis pathway for said "product" which could be part of a metabolic pathway is an essential pathway for viability. However, if said "product" is comprised in the growing medium, then biosynthesis of said "product" can be redundant and thus the biosynthesis pathway for said "product" is not anymore essential for viability.

Due to this inaccuracy the true scope of the claim(s) is not clear and can thus not be searched.

Even if one would consider the claim clear, it would still not be in accordance with the requirements of the PCT since, due to the above mentioned breadth (ANY microorganism, ANY metabolic pathway) it would embrace too many possibilities not being substantially supported by the description. The same applies to claims 2 and 3.

As a consequence, the search has been limited to the specific example disclosed in the description namely the attenuation of Mycobacterium through the inhibition of a kinase in particular the pKnG kinase.

**Re Item V**

1. Reference is made to the following document/s:  
D1: KOUL A ET AL: 'SERINE/THREONINE PROTEIN KINASES PKNF AND PKNG OF MYCOBACTERIUM TUBERCULOSIS: CHARACTERIZATION AND LOCALIZATION' MICROBIOLOGY, SOCIETY FOR GENERAL

MICROBIOLOGY, READING, GB, vol. 147, no. 8, August 2001 (2001-08),  
pages 2307-2314, XP001162730 ISSN: 1350-0872

D2: AV-GAY Y ET AL: 'The eukaryotic-like Ser/thr protein kinases of  
Mycobacterium tuberculosis' TRENDS IN MICROBIOLOGY, ELSEVIER  
SCIENCE LTD., KIDLINGTON, GB, vol. 8, no. 5, May 2000 (2000-05), pages  
238-244, XP002191211 ISSN: 0966-842X

2. The present application allegedly refers to a method for attenuating microorganisms, in particular Mycobacterium tuberculosis. However such an attenuation has not been demonstrated.

According to the disclosure it was merely identified that the already known PknG kinase of M. tuberculosis phosphorylates the enzyme isocitrate dehydrogenase (icd1), an enzyme which directs isocitrate to the TCA/Krebs cycle. Furthermore it could be derived by measuring the formation of NADPH (see description p.12, I.28 - p.13, I.10) that the isocitrate dehydrogenase (icd1) is inactivated through phosphorylation. However, these results do not demonstrate attenuation of the microorganism of interest.

Furthermore, it has to be noted that the relevance of PknG for the virulence of M. tuberculosis was already known from e.g., D1 or D2. Hence, PknG represent an obvious target for treating infections of M. tuberculosis or for attenuation of said organism.

Experiments were for example the activity of PknG has been inhibited (either by recombinant techniques [e.g., deletion of the gene] or by binding of compounds to PknG) leading to a lowered virulence/viability of the bacterium could have been performed in order to prove attenuation.

Consequently, methods to attenuate microorganisms and in particular M. tuberculosis are not substantially supported by the description (Article 5 PCT). Furthermore, the problem to attenuate a microorganism is not solved and thus no inventive activity can be acknowledged for such subject-matter (Article 33(3) PCT).

Compounds which bind to either PknG or Icd1 were not found and hence claim 12 and the claims relating to methods for identifying such compounds (claims 8-11) are neither substantially supported by the description nor solve convincingly any

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technical problem.

In view of the arguments above, claims 4-12 are not in accordance with Articles 5 and 33(3) PCT.

3. The intention to inhibit the isocitrate dehydrogenase (icd1) in claim 5 appears to be incorrect since such an inhibition would not lead to the requested effect (of attenuation) but rather to the opposite. Hence, said claim lacks clarity (Article 6 PCT).
4. The references given in the claims to preceding claims are very often wrong. Examples therefor are claims 2 or 4. Such claims do not fulfill the requirements of Article 6 PCT.

**Re Item VI**

1. Certain published documents (Rule 70.10):

| Application No<br>Patent No | Publication date<br>(day/month/year) | Filing date<br>(day/month/year) | Priority date (valid claim)<br>(day/month/year) |
|-----------------------------|--------------------------------------|---------------------------------|---|
| WO03/074728                 | 12.09.2003                           | 03.03.2003                      | 04.03.2002                                      |
| WO03/084947                 | 16.10.2003                           | 09.04.2003                      | 09.04.2002                                      |